You Don’t Look a Day Over 50 – Do Your Arteries?
Using Ultrasound to Evaluate Arterial Age

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Conflict of Interest Disclaimer

• Research grants
  – Siemens Medical Solutions
  – Sonosite

• Intellectual property royalties
  – WARF (carotid US and CVD risk prediction)
He looks 50.

But his arteries are pushing 70.

RBIF cIMT Mean = 0.671 mm
RBIF cIMT Max = 0.854 mm
Cardiovascular (CV) Disease
The Problem in the United States

- Each year, approximately 1.2 million Americans have a heart attack – 1/3 die
- Every day, nearly 1800 Americans die of CV disease

= 1 heart attack every 20 seconds
= 1 death every 48 seconds
The Diagnosis of Heart Disease Frequently Comes Too Late …

*First Symptom* of Heart Disease is *Heart Attack or Death*

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How Do We Determine Who is at Risk?

- Risk factors
- Treadmill stress testing
- Newer tests
Major Risk Factors for CV Disease

• Non-modifiable
  – Aging
  – Gender
  – Family history

• Modifiable
  – High cholesterol
  – High blood pressure
  – Cigarette smoking
  – Diabetes mellitus
  – Adverse lifestyle habits
INTERHEART
Risk of Heart Attack

- All risk factors = 90%
- All lifestyle = 63%

So What’s The Problem?

• Risk factors accurately predict risk in populations, but may not be adequate in individuals.

• At every level of risk factor exposure, substantial variation in degree of atherosclerosis:
  – Genetic susceptibility (e.g. family history)
  – Lifestyle habits
  – Duration of exposure
Treadmill Stress Testing
“But She Just Passed A Stress Test!”

Most Heart Attacks are Caused by Minor Blockages

Adapted from Falk E, et al. Circulation, 1995
The Plumbing Problem
Stress Testing Doesn’t Identify Minor Blockages
Transition to a Heart Attack

Transition to Acute Coronary Syndrome
The Challenge: How Can We Safely Look Into Your Arteries?
CT Angiography

Diagnostic test for people with chest pain - Not a screening test
The Solution:
Look at the Carotid Arteries

- Carotid arteries are a “window” to the coronary arteries
- Same risk factors
- Atherosclerosis of the carotid and coronary arteries ≅ any two coronary arteries

The Technique: Carotid Ultrasound
A Solution: Ultrasound Assessment of Carotid Intima-Media Thickness (IMT)
Measurement of Carotid IMT

- RCCA cIMT (opt. angle) Mean = 0.569 mm
- RCCA cIMT (opt. angle) Max = 0.802 mm
Carotid Ultrasound: Window To The Heart
Carotid Artery Duplex Ultrasound
Advantages of Carotid Ultrasound as a Risk Prediction Tool

- Completely noninvasive – no radiation, no harmful exposures, no known biological effects
- Identifies range of disease – increased CIMT, non-occlusive plaque, stenosis
- Predicts future heart attacks, death from heart disease, and stroke, with incremental predictive power
- Track serial changes
- Recommended by NCEP, AHA, ACC, ASE, SVM, and ESC to assist with CVD risk assessment
Carotid IMT Predicts Heart Attacks and Death from Heart Disease

Carotid IMT Predicts Future Strokes

Age and Gender adjusted Stroke incidence/1000 pt-yr

ASE CONSENSUS STATEMENT

Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force

Endorsed by the Society for Vascular Medicine

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Determination of “Vascular Age”
Determination of “Vascular Age”
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Determination of “Vascular Age”
Vascular Age Alters CV Risk

Change in Predicted 10-Year CHD Risk

- Substituting VA ↑ CHD risk in 37 (46%); ↓ in 17 (20%)
- Intermediate risk: 36% re-classified higher, 14% lower risk

N = 82, mean 55.8 yo, Framingham risk = 9.4%

Vascular Age Alters CV Risk In Untreated Intermediate Risk Patients

Why Not More?

Barriers to Clinical Use

• Small measurements: <1 pixel
  – High-end ultrasound instrumentation
  – Highly standardized protocols for performing and interpreting studies → highly trained scanners and readers

• Time-consuming
• Expensive
• No insurance reimbursement
• Results not integrated with treatment
Solution #1: Insurance Coverage

- Medicare 0126T
- Local carriers
- Office practice
  - Non-sonographer clinicians
  - Abbreviated scanning protocols
  - Border detection programs
Solution #2: Less Expensive Instrumentation
Solution #3: Abbreviated Scanning Protocols

Traditional Risk Assessment → “Intermediate” Risk → Plaque Screen

- Plaque Present
  - Intensify treatment
  - CCA CIMT optional

- Plaque Absent
  - CCA CIMT Measurement

Solution #4: Border Detection Programs

- Improve reproducibility
- Decrease reading time, esp. for less experienced reader

Why Might Atherosclerosis Imaging Help Get Patients to Goal?

- Pop psychologist thinks it will “motivate” the patient to “get with the program” or “take his health seriously”
- Rationale for providing personalized biomarker feedback is to identify a threat and use that to affect behaviors on a deeper emotional or subconscious level
- “Teachable moment” concept: increased readiness for change after life-threatening event
It Just Makes Sense, Doesn’t It?

• “You need to *scare* him so he starts taking his medicines.”

• “I hope this *scare* will make him finally take off some weight.”

• “I’m going to show him a picture of his artery – that will get his attention.”

• *It makes sense to doctors.*
Limitations of All New Non-Invasive Imaging Tests for CVD Risk Assessment

- Limited data that using these tests in clinical practice improves patient outcomes
  - Moderate evidence that they change physician behavior – aspirin, cholesterol medications
  - Some evidence that they may affect patient motivations, intentions, and in some studies adherence - inconsistent
Solution #6: Integration With Clinical Practice

- OPACA, Phase III
- N = 253, 58.1 (6.6) years old
- Framingham 10-year CV risk = 6.1 (5.2)%
- When ↑ CIMT or plaque were detected, physicians were more likely to prescribe:
  - Aspirin (OR 6.3 and 4.8, p<0.001)
  - Lipid-lowering therapy (OR 2.9 and 7.4, p<0.001)

OPACA Phase III

- Subjects with abnormal findings were more likely to report increases in:
  - Plans to take lipid-lowering medication (p=0.002)
  - Perceived likelihood of having (p=0.004) or developing (p<0.001) heart disease

- Even subjects without ultrasound abnormalities reported increased motivation to exercise (p=0.003) and make dietary changes (p=0.051)

Commercial Community Screening Programs

- Not CIMT test
- Not evidence-based – screen anyone
  - Scare tactics
  - Recommend repeat exams
- Limited physician supervision
- Patient ordered
- Quality control

"I am thankful to the Lord and Life Line Screening for saving my husband's life."
Sandra & Bob Waguespack
Roswell, GA
Rock crystal sphere, on a Japanese silver stand. 19th century China.
Carotid Artery Screening
What Will the Future Bring?

• Office-based testing
• Non-sonographer clinicians
  – Portable devices
  – Semi-automatic border detection
• Need research to identify types of patients who will benefit from screening
• Need proof that finding disease early really helps
Inferior doctors treat the full blown disease.
Mediocre doctors treat the disease before evident.
Superior doctors prevent the disease.

- Huang Dee: Nai-Ching (2600 B.C. 1st Chinese Medical Text)
Back up
Understanding The Effects of Personal Information on Behavior

• Used to counteract perceptions of invulnerability to health consequences of adverse behavior

• Raising threat perception and fear can motivate behavioral change

• Extended Parallel Process Model: people engage in protective behaviors when they
  – Perceive themselves to be at risk of a threat (threat appraisal), and
  – Feel they can reduce the threat (efficacy appraisal)

Understanding The Effects of Personal Information on Behavior

• **Step 1: Threat appraisal**
  – How severe is the threat?
  – How susceptible am I?

• **Step 2: Efficacy appraisal**
  – Assess ability to perform a behavior (**self-efficacy**)
  – That can avert the threat (**response efficacy**)

• **When both are high**
  – Danger control processes lead to acceptance of a threat message (**i.e. “stop smoking”**) 
  – Fear from threat appraisal may lead to a behavioral solution (**i.e. cessation**) 

Understanding The Effects of Personal Information on Behavior

- **But:** when threat appraisal is high and efficacy appraisal is low
  - Fear may lead to a cognitive solution (*i.e.* avoidance)
  - Fear control processes may lead to rejection of the threat message

- Personalized biomarker feedback showing harm may have **maximal effect if visual**, by avoiding “disengagement beliefs” that distort meaning of potentially motivating information

- **But if self-efficacy is low, motivational change is unlikely**

Biomarker Feedback and Psychology in Action: Smoking Cessation

• A small study (N=153) randomly assigned smokers to SC or SC + carotid ultrasound, with a picture of their plaques
• Smoking cessation rates were 22.2% in those with plaques (p=0.003)
• Follow-up pilot RCT (N=23), visual vs. verbal feedback, the intervention increased
  – Perception of smoking-related illness
  – Smoking cessation behavior and intention
• **Mediated by self-efficacy**: intention only increased in people with high levels (p<0.03)

Solution #6:
Integration With Clinical Practice OPACA
Phase III

- N = 253, 58.1 (6.6) years old
- Framingham 10-year CV risk = 6.1 (5.2)%
- When ↑ CIMT or plaque were detected, physicians were more likely to prescribe:
  - Aspirin (OR 6.34 and 4.84, p<0.001)
  - Lipid-lowering therapy (OR 2.93 and 7.40, p<0.001)

OPACA Phase III

- Subjects with abnormal findings were more likely to report increases in
  - Plans to take lipid-lowering medication (p=0.002)
  - Perceived likelihood of having heart disease (p=0.004)
  - Perceived likelihood of developing heart disease (p<0.001)

- Even subjects without ultrasound abnormalities reported increased motivation to exercise (p=0.003)

Is Treatment Justified?

Statin Therapy in “Low Risk” Patients

- METEOR
- N = 984 subjects
- Only risk factor = age
- OR
- FRS <10%
- Focal CIMT >1.2 mm
- LDL-C 120-190 mg/dL

Crouse JR, et al.  JAMA 2007; 297;1344
### CIMT Regression on Statin Therapy Predicts CV Event Reduction

<table>
<thead>
<tr>
<th>Trial (N)</th>
<th>Statin</th>
<th>Δ CIMT Progression (mm/yr)</th>
<th>CVD Event</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS (N=919)</td>
<td>Lovastatin</td>
<td>-0.015 (p=0.001)</td>
<td>CVD Death, MI, Stroke</td>
<td>0.34 [0.12, 0.69]</td>
</tr>
<tr>
<td>KAPS (N=447)</td>
<td>Pravastatin</td>
<td>-0.014 (p=0.005)</td>
<td>CVD Death, MI, Stroke</td>
<td>0.57 [0.22, 1.47]</td>
</tr>
<tr>
<td>PLAC-II (N=151)</td>
<td>Pravastatin</td>
<td>-0.009 (p=0.44)</td>
<td>Clinical Coronary Events</td>
<td>0.37 [0.11, 1.24]</td>
</tr>
<tr>
<td>CAIUS (N=305)</td>
<td>Pravastatin</td>
<td>-0.014 (p=0.0007)</td>
<td>CVD Death, MI</td>
<td>1.02 [0.14, 7.33]</td>
</tr>
<tr>
<td>REGRESS (N=255)</td>
<td>Pravastatin</td>
<td>-0.030 (p=0.002)</td>
<td>Clinical Events</td>
<td>0.51 [0.24, 1.07]</td>
</tr>
<tr>
<td>BCAPS (N=793)</td>
<td>Fluvastatin</td>
<td>-0.008 (p=0.002)</td>
<td>CVD Death, MI, Stroke</td>
<td>0.64 [-0.24, 1.66]</td>
</tr>
<tr>
<td>FAST (N=164)</td>
<td>Pravastatin</td>
<td>(p&lt;0.001)</td>
<td>CVD Death, MI</td>
<td>0.32 [0.10, 1.06]</td>
</tr>
<tr>
<td><strong>Pooled Estimate</strong></td>
<td></td>
<td><strong>-0.012 [-0.016, -0.007]</strong></td>
<td></td>
<td><strong>0.48 [0.30, 0.78]</strong></td>
</tr>
</tbody>
</table>

*95% CI, estimate excludes FAST

# Prospective Studies Relating CIMT to Incident CV Events in Asymptomatic Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Yrs</th>
<th>CV Event</th>
<th>Cutpoint</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>12,841</td>
<td>45-64</td>
<td>5</td>
<td>MI, CHD death</td>
<td>tertile</td>
<td>W: 2.53 (1.02-6.26) M: 2.02 (1.32-3.09)</td>
</tr>
<tr>
<td></td>
<td>14,214</td>
<td>45-64</td>
<td>7</td>
<td>stroke</td>
<td>tertile</td>
<td>W: 2.32 (1.09-4.94) M: 2.24 (1.26-4.00)</td>
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<tr>
<td>CAPS</td>
<td>5,056</td>
<td>19-90</td>
<td>4</td>
<td>MI, stroke, death</td>
<td>quartile</td>
<td>1.85 (1.09-3.15)</td>
</tr>
<tr>
<td>CHS</td>
<td>4,476</td>
<td>&gt;65</td>
<td>6</td>
<td>MI</td>
<td>quintile</td>
<td>3.61 (2.13-6.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stroke</td>
<td>quintile</td>
<td>2.57 (1.64-4.02)</td>
</tr>
<tr>
<td>KIHD</td>
<td>1,257</td>
<td>42-60</td>
<td>3</td>
<td>MI</td>
<td>&gt;1.0 mm</td>
<td>2.1 (0.8-5.2)</td>
</tr>
<tr>
<td>Yao City</td>
<td>1,289</td>
<td>60-74</td>
<td>5</td>
<td>stroke</td>
<td>quartile</td>
<td>4.9 (1.9-12.0)</td>
</tr>
<tr>
<td>MDCS</td>
<td>5,163</td>
<td>46-68</td>
<td>7</td>
<td>MI, CHD death</td>
<td>tertile</td>
<td>1.50 (0.81-2.59)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>6,389</td>
<td>&gt;55</td>
<td>7-10</td>
<td>MI</td>
<td>quartile</td>
<td>1.95 (1.19-3.19)</td>
</tr>
</tbody>
</table>

Prospective Studies Relating Carotid Plaque Presence to Incident CV Disease in Asymptomatic Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Yrs</th>
<th>Event</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>12,375</td>
<td>45-64</td>
<td>7</td>
<td>MI, CHD death</td>
<td>2.96 (1.54-3.30)</td>
</tr>
<tr>
<td>KIHD</td>
<td>1,288</td>
<td>42-60</td>
<td>≤2</td>
<td>MI</td>
<td>4.15 (1.5-11.47)</td>
</tr>
<tr>
<td>MDCS</td>
<td>5,163</td>
<td>46-68</td>
<td>7</td>
<td>MI, CHD death</td>
<td>1.81 (1.14-2.87)</td>
</tr>
<tr>
<td>Yao City</td>
<td>1,289</td>
<td>60-74</td>
<td>5</td>
<td>Stroke</td>
<td>3.2 (1.4-7.1)</td>
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<tr>
<td>Northern Manhattan</td>
<td>1,939</td>
<td>&gt;40</td>
<td>6</td>
<td>Stroke</td>
<td>3.1 (1.1-8.5)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>6,389</td>
<td>&gt;55</td>
<td>7-10</td>
<td>MI</td>
<td>1.83 (1.27-2.62)</td>
</tr>
</tbody>
</table>